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Rubinstein-Taybi Syndrome Caused by a De Novo Reciprocal Translocation t(2;16)(q36.3;p13.3)

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Rubinstein-Taybi syndrome (RTS) is a multiple congenital anomalies and mental retardation syndrome characterized by facial abnormalities, broad thumbs, and broad big toes. We have shown previously that disruption of the human CREB-binding protein (*CBP*) gene, either by gross chromosomal rearrangements or by point mutations, leads to RTS. Translocations and inversions involving chromosome band 16p13.3 form the minority of *CBP* mutations, whereas microdeletions occur more frequently (~10%). Breakpoints of six translocations and inversions in RTS patients described thus far were found clustered in a 13-kb intronic region at the 5′ end of the *CBP* gene and could theoretically only result in proteins containing the extreme N-terminal region of CBP. In contrast, in one patient with a translocation t(2;16)(q36.3;p13.3) we show by using fiber FISH and Southern blot analysis that the chromosome 16 breakpoint lies about 100 kb downstream of this breakpoint cluster. In this patient, Western blot analysis of extracts prepared from lymphoblasts showed both a normal and an abnormal shorter protein lacking the C-terminal domain, indicating expression of both the normal and the mutant allele. The results suggest that the loss of C-terminal domains of CBP is sufficient to cause RTS. Furthermore, these data indicate the potential utility of Western blot analysis as an inexpensive and fast approach for screening RTS mutations. Am. J. Med. Genet. 92:47–52, 2000.

KEY WORDS: Rubinstein-Taybi syndrome; chromosome 16; translocation; fiber FISH; Western blot analysis

INTRODUCTION

The main clinical manifestations of Rubinstein-Taybi syndrome (RTS) (MIM: 180849) are mental retardation, broad thumbs, broad big toes, and facial abnormalities [Rubinstein and Taybi, 1963]. We have shown previously that RTS is associated with mutations in the CREB-binding protein gene (*CBP*) [Petrij et al., 1995]. In all cases the other allele is normal, which led us to hypothesize that RTS is caused by haploinsufficiency of CBP [Petrij et al., 1996, 2000b]. CBP and the related protein p300 are transcriptional cofactors which modulate the expression of numerous genes and thereby play an important role in differentiation, cell growth, and development. CBP may stimulate transcription by its intrinsic and associated histone acetyltransferase (HAT) activity, which helps open the chromatin structure, allowing easier access of sequence-specific transcription factors to DNA. In addition, cofactors such as CBP may also stimulate gene expression by functioning as bridging factors between site-specific transcription factors and factors of the basal transcriptional machinery. To date, many different factors binding to CBP have been identified (selected factors are depicted in Figure 2).

Because no missense mutations affecting specific CBP domains have yet been identified, there are no indications as to which domains are critical in the development of the RTS phenotype. In at least nine of the reported 33 microdeletions the entire *CBP* gene has been deleted [Petrij et al., 2000a]. In addition, we found

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four truncating mutations after analysis of 37 patients by the protein truncation test (PTT), resulting in N-terminally truncated proteins [Petrij et al., 2000a]. The identification of additional mutations may provide more insight as to whether the loss of specific CBP functions causes RTS.

However, since *CBP* has a relatively large transcript (~8 kb), the commonly used assays such as PTT and single-stranded conformation polymorphism analysis (SSCA) are tedious and costly to perform. If Western blot analysis could detect mutations in CBP, this assay could be used as a (pre-)screening tool for the detection of *CBP* mutations. In this article, we describe an extensive analysis, including Western blot assays, of a *CBP* mutation in an RTS t(2;16) case with a breakpoint more distal than all other known translocation and inversion breakpoints and discuss the implications of the detected truncated protein.

CLINICAL REPORT

The t(2;16) propositus was the second-born child of healthy and nonconsanguineous Dutch parents. The translocation breakpoint was briefly mentioned by us in previous reports [Petrij et al., 1995; Giles et al., 1997a]. The clinical history of the child was typical for RTS, including prolonged feeding problems, recurrent respiratory infections, constipation, and moderate to severe psychomotor retardation. Pertinent physical findings at 4 years of age included short stature, microcephaly, highly arched eyebrows, long eyelashes, left side cataract, nasal septum well below the alae, highly arched palate, retrognathia, and small and low-set ears (Fig. 1A,B). There was generalized hirsutism and he had a bilateral cryptorchidism. He had broad thumbs, broad halluces, and hyperlax ligaments (see also Fig. 1C,D).

Cytogenetic Analysis

The patient was karyotyped using standard cytogenetic methods followed by metaphase FISH analysis with one or more cosmid probes from the *CBP* gene. One or two color FISH was performed as described previously [Kievits et al., 1990; Driesen et al., 1991; Dauwerse et al., 1992; Giles et al., 1997a]. Probe RT1 (D16S237) was labeled in red (Texas Red). A chromosome 16-specific centromeric probe pHUR195 was cohybridized.

Fiber FISH was used to determine the position of the chromosome 16 breakpoint of the t(2;16) case more precisely. Extended chromatin fibers were produced according to the methods described by Giles et al. [1997a]. Cosmids RT1, RT102, and RT191 were labeled with alternating haptens, allowing dual color detection of hybridization; 50 extended fibers were examined.

Western Blot Analysis

Total protein was isolated from EBV-transformed lymphoblastoid cell lines. Briefly, cells were collected by centrifugation and washed with PBS (PBS: 150 mM NaCl, 9.9 mM $Na_2HPO_4.2H_2O$, 1.6 mM KH_2PO_4). The cells were subsequently resuspended in lysis buffer (50 mM Tris-HCl pH 7.4, 250 mM NaCl, 0.1% Triton X100, 5 mM EDTA) containing protease inhibitors (phenylmethylsulfonylfluoride [PMSF], trypsin inhibitor, and leupeptin) and incubated for 30 min on ice. Every 10 min the tubes were vortexed. The supernatant was cleared by centrifugation at 10.000 rpm for 15 min at 4°C. Protein concentration was determined by the Bradford assay (Bio-Rad, Cambridge, MA). The pellet was resuspended in an equal volume of Laemmli sample buffer [Harlow and Lane, 1988] and boiled for 10 min. For immunoblot analysis, 70 μg of each extract was loaded on a 8% SDS-polyacrylamide gel, electrophoresed, and transferred to nitrocellulose (Schleicher and Schnell, Keene, NH) using the wet electrophoretic transfer procedure for high molecular weight proteins as described previously [Harlow and Lane, 1988]. The incubation with antibodies and the enhanced chemoluminescence procedure were performed essentially as described previously [De Rooij et al., 1996]. Polyclonal antibody A-22 (Santa Cruz Biotechnology, Santa Cruz, CA) interacts with the N-terminus of CBP; CBD (kindly provided by R. Goodman) with the C-terminal part of the CREB-binding domain (CBD), and NM11 (Pharmingen, San Diego, CA) [see Dallas et al., 1997] with the C-terminal part of the second transactivation domain (TAD) of CBP. In initial experiments both the supernatant and the pellet were analyzed. The vast majority of CBP was, however, present in the supernatant. For further analysis only the supernatant was used.

RESULTS

The patient had clinical findings typical of RTS. In Figure 1A,B the face is shown from the lateral (A) and frontal (B) side, respectively, whereas Figure 1C shows the broad halluces of the right foot and Figure 1D the broad thumb of the left hand (all at the age of 2.5 years). The facial 'gestalt' is characteristic for children with RTS at that age.

Karyotyping of the patient had already shown a translocation t(2;16)(q36.3;p13.3) (see Fig. 1H for a schematic representation). We refer to this patient as $t(2;16)^{NL}$ to avoid confusion with another RTS t(2;16) patient [Imaizumi and Kuroki, 1991]. In a metaphase FISH experiment with probe RT1 the translocation was confirmed [Petrij et al., 1995]. Figure 1E shows that this chromosome 16 probe (in red) is translocated to the derivative chromosome 2. Parental chromosomes were normal (not shown). To determine the location of the breakpoint in more detail, we performed a fiber FISH experiment. Cosmids RT1 and RT191 were labeled in red and the connecting cosmid RT102 in green; the overlap between cosmids can be seen as yellow. More than 50 DNA threads were examined. Two representative fibers are shown in Figure 1F. The DNA thread of the normal chromosome 16 (on the left) starts (on top) with the red RT1 signal, followed successively by the small yellow signal of the RT1/RT102 overlap, the green RT102 signal, the larger yellow signal of the RT102/RT191 overlap, and finally by the remaining (red) part of RT191. The DNA thread of derivative chromosome 16 starts with the red RT1 signal, which is followed by the small yellow signal of the RT1/RT102

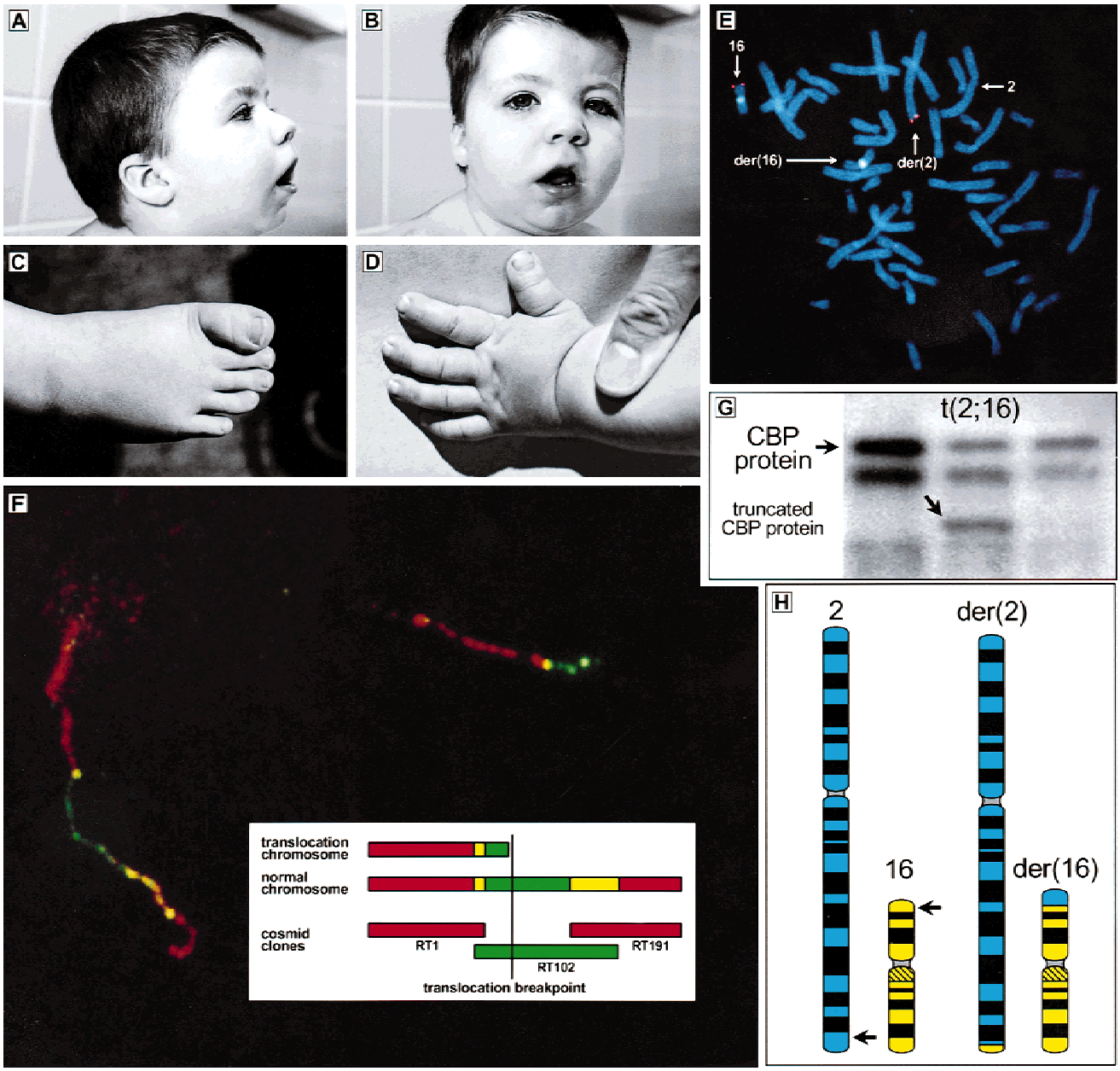

Fig. 1. Dutch RTS patient with a t(2;16) at the age of 2.5 years: lateral face (**A**); frontal face (**B**); right foot (**C**) and left hand (**D**) (see text); metaphase FISH which shows that the RT1 signal (in red) is translocated from der(16) to der(2) (**E**); chromosomes 16 are marked by a specific centromeric probe; fiber FISH showing that the translocation breakpoint lies within cosmid RT102 (**F**) (see text); Western blot analysis showing a truncated CBP protein (**G**); schematic representation of the translocation (**H**).

overlap, but in contradiction to the normal chromosome 16 the green signal of RT102 is interrupted after a short stretch. These results indicate that the breakpoint is located in the distal part of RT102. Southern analysis confirmed these data because the $t(2;16)^{NL}$ breakpoint maps to a 5.4 kb *Eco*RI fragment of RT102 (see Fig. 2 and Petrij et al. [1995]). Juxtaposing the location of this *Eco*RI fragment against the intron-exon structure of *CBP* (GenBank Accession numbers AC004651 and U85962), it can be calculated that the breakpoint lies between exons 16 and 17 (intron 16); consequently, the protein will be truncated at amino acid 1084.

Furthermore, we tested whether we could detect stable protein produced by the *CBP* gene from the wild-type or mutant alleles. To this end, protein extracts were prepared from several patient-derived EBV-transformed lymphoblasts followed by Western blot analysis. To detect CBP, we primarily used polyclonal antibody A-22 which was raised in rabbits against the extreme N-terminus of CBP. This antibody does not cross-react with the related p300 protein, which migrates at the same position as CBP in SDS-polyacrylamide gels, but does detect a band of unknown origin in the 250 kDa region of the gel. In healthy individuals this band is always detected, and

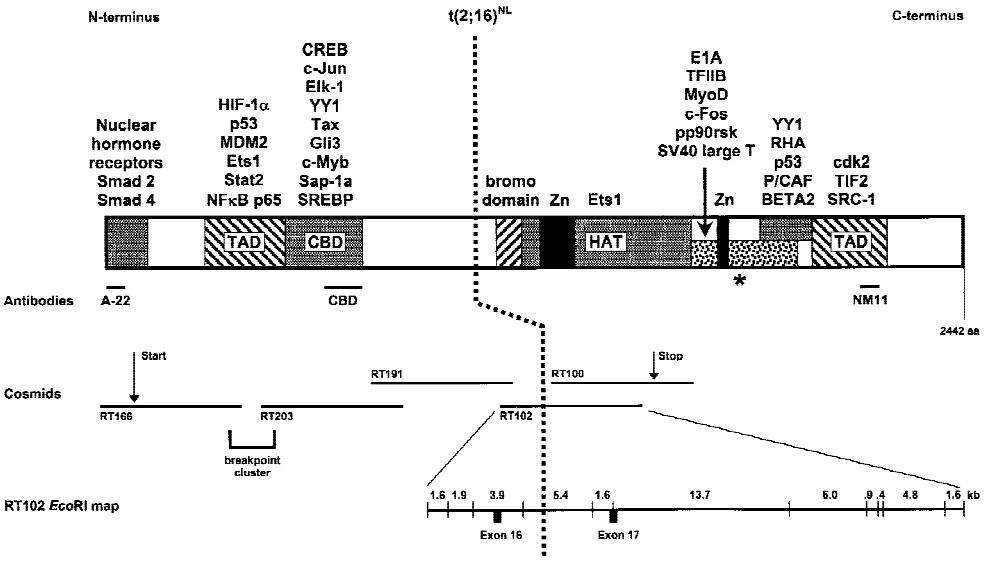

Fig. 2. Structure of the CBP protein and the location of the RTS t(2;16) breakpoint. The proteins found to interact with CBP and/or the related factor p300 are indicated. (Gli3, Dai et al. [1999]; BETA2, Mutoh et al. [1998]; p53, Avantaggiati et al. [1997] and Lill et al. [1997]; RHA, Nakajima et al. [1997]; MDM2, Grossman et al. [1998]; Ets-1, Yang et al. [1998]; NFκB p65, Gerritsen et al. [1997]; see Giles et al. [1997a, 1998] for review and references of all other mentioned interacting proteins.) The epitopes of antibodies A-22, CBD, and NM11 are depicted. Zn = zinc-finger; TAD = transactivation domain; CBD = CREB-binding domain; HAT = histone acetyltransferase domain; * = protein kinase A phosphorylation site. Human CBP contains 2442 amino acid residues (aa). The open reading frame of the human CBP transcript is 7.3 kb and covers from start (ATG) to stop (TAG) 146 kb of genomic DNA. The orientation of the gene is from centromere to telomere and it consists of 31 exons. The t(2;16) breakpoint is positioned between exons 16 and 17. The gene area is cloned in five cosmids. Between cosmids RT166 and RT203 (intron 2) a small ~5 kb area within the breakpoint cluster is still uncloned [Giles et al., 1997a; Petrij, 2000]. Note that the five cosmids are not drawn under the corresponding protein domains.

presumably represents a cross-reacting protein. With antibody A22 a band is visible at the expected position of approximately 300 kDa in all cases (Fig. 1G). Additionally, in the t(2;16)^{NL} case an extra band is visible in the region above the 112 kDa marker protein, suggesting the presence of truncated CBP. The identification of the upper band as full length CBP was confirmed by stripping the blot and subsequent incubation with mouse monoclonal antibody NM11, which recognizes an epitope spanning amino acids 2071–2091 near the C-terminus of CBP [Dallas et al., 1997] (results not shown). The extra band in the t(2;16)^{NL} case can also be detected with rabbit polyclonal antibody CBD which was raised against the CREB-binding domain encompassing aa 571–682, but not with NM11 (results not shown) (see Fig. 2 for antibody positions). These results indicate that the >112 kDa band indeed represents a truncated CBP protein.

DISCUSSION

All detected RTS translocation and inversion breakpoints, with the notable exception of the RTS translocation t(2;16)^{NL}, map to the 5′ part of the *CBP* gene, the so-called breakpoint cluster region. CBP is also involved in acute myeloid leukemia (AML) associated with the somatic translocation t(8;16)(p11;p13.3), in which a large part of *CBP* is fused to a putative acetyl transferase gene called monocytic leukemia zinc finger (*MOZ*) on 8p11 [Giles et al., 1995, 1997b; Borrow et al., 1996] and in treatment-related hematological malignancies associated with a somatic t(11;16)(q23;p13) in which *CBP* is fused to a gene called mixed lineage leukemia (*MLL*) on 11q23 [Rowley et al., 1997; Sobulo et al., 1997]. All but one (11/12) of the chromosome 16 breakpoints in hematological malignancies with a rearranged *CBP* are located within the breakpoint cluster region. The DNA region rearranged in the t(2;16)^{NL} patient may represent, however, a second region of *CBP* that is prone to rearrangements, since one t(11;16) breakpoint is located in the same region (amino acid 1021 in exon 16) [Sobulo et al., 1997; Giles et al., 1998] as the t(2;16)^{NL} RTS case presented here (intron 16).

All RTS translocations and inversions, except for the t(2;16)^{NL}, could theoretically only produce proteins containing a very small part of the N-terminus of CBP (266 amino acids or less). In the case of the (2;16)^{NL}, a stable truncated protein of half the normal length in addition to the expression of the wild-type allele resulted in a child with characteristics of RTS. Because the protein observed from the Western analysis (slightly larger than 112 kDa) corresponds with the predicted protein size (119 kDa) generated by this translocation, we do not expect that the translocation results in the fusion of CBP with another protein. It is unknown whether N-terminal functions are affected, for instance, by aberrant folding of the truncated protein. However, one intriguing possibility is that the C-terminus of CBP is necessary for normal development. The truncated t(2;16)^{NL} CBP protein, in any event, lacks various functional domains including its histone acetyltransferase (HAT) domain and the binding domain for the histone acetyltransferase P/CAF, which probably results in the total loss of CBP's function in chromatin remodeling. However, other regions binding to transcriptional regulators or cell cycle proteins have also been lost, such as the E1A-binding domain, which also binds the basal transcription factor TFIIB, and the region binding

transcription-factor SRC1. At this stage, it is not possible to link RTS to the loss of any specific function of CBP. However, the identification of this patient expressing a C-terminally truncated CBP has already delineated potential candidate domains.

In 1999 Oike et al. reported on a mouse model for RTS. In contrast to the *hemizygous* null mutant of Tanaka et al., [1997], Oike constructed heterozygous mice with one *CBP* allele producing protein truncated at amino acid 1085. By chance, this position in the mouse exactly corresponds to amino acid 1084 in humans, and is thereby a perfect model for our $t(2;16)^{NL}$ RTS patient. Oike et al.'s mutant animals have many traits reminiscent of RTS, such as growth retardation (100%), poor locomotor activity (100%), retarded osseous maturation (100%), large anterior fontanel (100%), hypoplastic maxilla with narrow palate (100%), cardiac abnormalities (17%), and skeletal abnormalities (7%). However, broad digits were not observed in either Oike et al.'s [1999] or Tanaka et al.'s [1997] mice. Tanaka et al.'s mutant showed a milder phenotype, although growth retardation (33%), large anterior fontanel (67%), and other skeletal abnormalities such as distinct holes in the xiphoid process (29%) were reported. Oike et al. [1999] suggest that the phenotypic difference could be explained by dominant negative effects, as opposed to haploinsufficiency. Our patient does not have a significantly more severe phenotype than other RTS patients. Moreover, when compared with three patients with defined hemizygous deletions affecting the entire *CBP* gene [Breuning et al., 1993; Hennekam et al., 1993; Petrij et al., 1995], no significant differences in phenotype were observed. We therefore cannot reach the same conclusions as Oike et al. [1999]. Whether a dominant negative effect of certain CBP mutations exists remains unanswered. Genetic background plays a critical role in RTS phenotype, and the extrapolation of results from mouse experiments to the human situation is always imperfect.

The setup of the Western blot approach was aimed to gain more insight into whether this approach could be used for diagnostic purposes or as a prescreening method of RTS patients. In preliminary experiments with SDS-PAGE gels of a higher percentages (10, 12.5, 15, and 20%) separating smaller proteins, we found that two known RTS point mutations (RT2848 and RT2991; see also Petrij et al. [1995]), which should result in relatively small truncated CBP proteins did not give clear signals in Western blot experiments with polyclonal antibody A-22 raised against the N-terminus of CBP, whereas for another $inv(16)^{NOR}$ case a truncated fragment could be detected (not shown). These data indicate that the truncated mRNAs are not always stable, perhaps due to nonsense-mediated decay. In agreement with the haploinsufficiency hypothesis, we observed in some cases, including the $(2;16)^{NL}$ case, lower levels of full-length CBP compared to control persons, as well as loading controls for each lane. The Western blot approach can thus be used for diagnostic purposes only as an ancillary approach. However, if protein extracts are made directly from blood, the Western blot approach is relatively simple, fast, and inexpensive, and may thereby be valuable for prescreening suspected RTS cases in research settings to select samples for further analysis. In particular, those cases that display a truncated band and/or lower levels of the CBP protein may be of interest for further analysis at the DNA level. The discovery of additional CBP mutations and ongoing animal experiments may ultimately provide more information on which domains of CBP are critically affected in RTS.

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